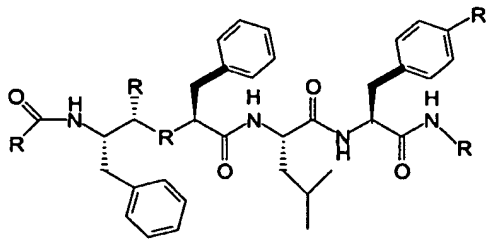
THE INVENTION CLAIMED IS

1. A method of treating tumors or proliferative disorders in an animal or human in need of such treatment, comprising administering to the animal or human therapeutically effective amounts in unit dosage form of a composition comprising a carrier and at least one secretase inhibitor.

2. The method of claim 1, wherein the secretase inhibitor specifically inhibits amyloid precursor protein secretases.

3. The method of claim 2, wherein the secretase inhibitor is a γ-secretase inhibitor.

4. The method of claim 3, wherein the γ-secretase inhibitor is an aspartyl protease transition-state γ-secretase inhibitor having the following backbone chemical structure:



wherein R refers to analogue substitutions.

5. The method of claim 4, wherein the aspartyl protease transition-state γ-secretase inhibitor is L-685,458.

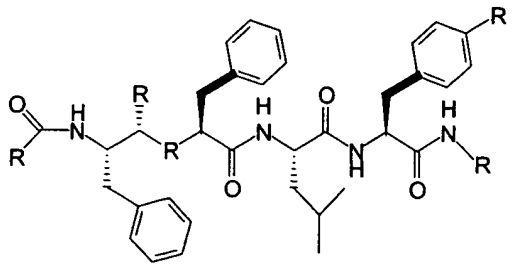
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(Guo, Q. et al., NeuroReport, 8, 379-383, 1996) and deficits in capacitative calcium entry (Leissring, M.A. et al., J. Cell Biol., 149, 793-798, 2000).

[0016] Notch signaling has been implicated as a regulatory feature of the angiogenic process (Zhong, T. et al., Nature, 414(6860), 216-220, 2001). Additionally, presenilin knockout mice (mice lacking one or both of the presenilin genes, thus displaying varying degrees of impairment in γ-secretase activity) suffer from abnormal vessel formation (Herreman A. et al., PNAS, 12, 11872-11877, 1999; Shen, J. et al., Cell, 89, 629-639, 1997), suggesting that γ-secretase activity may play a role during angiogenesis.

[0017] Thus, there exists a need for compounds that exhibit angiogenesis-inhibiting activity, which can inhibit the pathological angiogenesis observed in cancer and other angiogenic-related diseases, but which have minimal side effects and do not require an extended treatment period and/or combination therapy with other treatment modalities, such as chemotherapy or radiation.

BRIEF SUMMARY OF THE INVENTION

[0018] The present invention provides for the first time the discovery that compounds which inhibit γ-secretase and β-secretase, referred to as γ-secretase and β-secretase inhibitors, exhibit potent anti-angiogenic activity, and that administration of these inhibitors to animals or humans afflicted with disorders associated with pathological angiogenesis, such as cancer, proliferative disorders, or inflammatory disorders, inhibits the pathological angiogenesis observed in the afflicted animals or humans.

[0019] In particular, the present invention provides a method of treating tumors or proliferative disorders in animals or humans in need of such treatment by administering to the animal or human therapeutically effective amounts in unit dosage form of a composition containing a carrier and at least one γ-secretase or β-secretase inhibitor that inhibits secretase amyloid precursor protein (APP) processing.

[0020] The present invention also provides a method of inhibiting angiogenesis associated with tumors, proliferative or inflammatory disorders in animals or humans in need of such inhibition by administering to the animal or human therapeutically effective amounts in unit dosage form of a composition containing a carrier and at least one γ-secretase or β-secretase inhibitor that inhibits secretase APP processing.

[0021] Gamma-secretase inhibitors that are administered according to the method of the present invention can include, without limitation, aspartyl protease transition-state inhibitors,

such as L-685,458; dipeptide protease inhibitors, such as DAPT and DAPM; or isocoumarin-based serine protease inhibitors, such as JLK-6.

[0022] Beta-secretase inhibitors that are administered according to the method of the present invention can include, without limitation, peptidomimetic tight binding transition-state analogue inhibitors, such as OM99-2, or substrate analogue peptide inhibitors, such as Z-VLL-CHO GL189, or P10-P4'statV.

[0023] Tumors that can be treated according to the method of the present invention include, without limitation, malignant brain tumors, such as glioblastomas; malignant lung tumors, such as adenocarcinomas; or malignant tumors of the breast, colon, kidney, bladder, head or neck. Proliferative disorders that can be treated according to the method of the present invention include, without limitation, hematopoietic disorders, such as leukemias, lymphomas or polycythemias; ocular disorders, such as diabetic retinopathy, macular degeneration, glaucoma or retinitis pigmentosa. Inflammatory disorders that can be treated according to the method of the present invention include, without limitation, rheumatoid arthritis, osteoarthritis, pulmonary fibrosis, sarcoid granulomas, psoriasis or asthma.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Fig 1a: Effect of β and γ secretase inhibitors on the viability of human brain endothelial cells. The potential toxicity of various doses of β and γ secretase inhibitors was estimated by measuring LDH activity in the culture medium. ANOVA revealed no main effect for L-685,458 but a significant main effect for Z-VVL-CHO ($P<0.03$), OM99-2 ($P<0.006$) and DAPT ($P<0.009$). Post-hoc analysis did not show any significant difference between control and any of the β and γ secretase inhibitors tested ($P>0.05$) showing that the β and γ secretase inhibitors did not induce endothelial cell death at the doses employed.

[0025] Fig. 1b: Effect of β and γ secretase inhibitors on the proliferation of human brain endothelial cells. The amount of viable cells following 24 hours of treatment with various doses of b and g secretase inhibitors was measured using the Quick cell proliferation assay kit. ANOVA revealed a significant main effect of L-685,458 dose ($P<0.001$), of Z-VVL-CHO dose ($P<0.001$), of OM99-2 dose ($P<0.001$) and of DAPT ($P<0.001$). Post-hoc analysis showed significant differences between control and 2 μM L-685,458 ($P<0.001$), between control and 5 μM Z-VVL-CHO ($P<0.001$), control and 5 μM OM99-2 ($P<0.001$) and between control and 5 μM DAPT ($P<0.001$).

[0026] Fig 2a: Representative pictures showing the effect of L-685,458 and Z-VVL-CHO on capillary morphogenesis.